

**AMENDMENTS TO THE CLAIMS**

The following is a complete, marked-up listing of revised claims with a status identifier in parenthesis, underlined text indicating insertions, and strike through and/or double-bracketed text indicating deletions.

**LISTING OF CLAIMS**

1. (Original) A pseudo-thermosetting neutralized chitosan composition, which comprises 0.1 to 2.0 wt/v %, based on the total composition, of a homogeneously reacetylated chitosan derived from a chitosan having a deacetylation degree of 80-90 %, having a molecular weight of not smaller than 200 kDa and a deacetylation degree of 30-60 %, neutralized with an hydroxylated base, wherein said composition forms a phosphate free transparent hydrogel at a temperature higher than 5°C.

2. (Original) The pseudo-thermosetting neutralized chitosan composition according to claim 1, comprising 0.5 to 1 wt/v %, based on the total composition, of said homogeneously reacetylated chitosan.

3. (Currently Amended) The pseudo-thermosetting neutralized chitosan composition according to claim 1 ~~or 2~~, wherein the deacetylation degree of said homogeneously reacetylated chitosan is 45 to 55 %.

4. (Currently Amended) The pseudo-thermosetting neutralized chitosan composition according to ~~anyone of claims 1 to 3~~, wherein the molecular weight of said homogeneously reacetylated chitosan is not smaller than 600 kDa.

5. (Currently Amended) The pseudo-thermosetting neutralized chitosan composition according to ~~anyone of claims 1 to 4~~, further comprising a diol having a distance of at least 4.7 Å between its hydroxyl groups.

6. (Original) The pseudo-thermosetting neutralized chitosan composition according to claim 5, wherein said diol is 1,3-propanediol.

7. (Original) A process for producing a homogeneously reacetylated chitosan having a molecular weight of not smaller than 200 kDa and a deacetylation degree of 30-60 % which comprises the steps of:

a) filtrating a chitosan having a molecular weight of not smaller than 200 kDa and a deacetylation degree of 80 to 90 % dissolved in an acidic medium to eliminate insoluble particles;

b) precipitating chitosan contained in the filtrated acidic solution obtained in step a) to obtain chitosan free of insoluble particles;

c) preparing a cooled acidic solution of the chitosan free of insoluble particles obtained in step b) at a temperature lower than 5°C to obtain a cooled acidic solution of chitosan free of insoluble particles;

d) preparing a cooled acetic anhydride solution containing a predetermined amount of acetic anhydride in methanol at a temperature lower than 5°C;

e) reacetylating chitosan by adding dropwise, under homogeneous conditions, the cooled acetic anhydride solution of step d) to the cooled solution of chitosan prepared in step c) to provide a crude homogeneously reacetylated chitosan having a deacetylation degree of 30-60 %;

f) treating said crude chitosan obtained in step e) to eliminate salts produced during reacetylation and insoluble particles of chitosan to obtain a homogeneously reacetylated chitosan having a deacetylation degree of 30-60 %.

8. (Original) The process according to claim 7, wherein the treating step f) includes the steps of:

f-1) dialyzing chitosan obtained in step e) to eliminate salts produced during reacetylation in order to obtain a homogeneously reacetylated chitosan solution;

f-2) filtrating the chitosan solution obtained in step f-1) to eliminate insoluble particles of chitosan;

f-3) precipitating chitosan contained in the filtrated solution obtained in step f-2) and then drying chitosan to obtain a homogeneously reacetylated chitosan having a deacetylation degree of 30 - 60 %.

9. (Original) The process according to claim 8, wherein the precipitating step f-3) includes addition of a mixture of  $\text{NH}_4\text{OH}$ /methanol.

10. (Currently Amended) A homogeneously reacetylated chitosan having a molecular weight of not smaller than 200 kDa and a deacetylation degree of 30-60% obtained by the process as claimed in ~~anyone of~~ claims 7 to 9 for use in the preparation of a pseudo-thermosetting neutralized chitosan composition forming a phosphate-free transparent hydrogel at a temperature higher than 5°C.

11. (Original) A process for producing a pseudo-thermosetting neutralized chitosan composition forming a phosphate-free, transparent hydrogel at a temperature higher than 5°C, which comprises the steps of:

g) solubilizing a homogeneously reacetylated chitosan derived from a chitosan having a deacetylation degree of 80 - 90 %, having a molecular weight of not smaller than 200 kDa and a deacetylation degree of 30 - 60 %, in an

aqueous HCl medium and cooling said acidic chitosan solution at a temperature lower than 5°C;

h) neutralizing the cooled chitosan solution obtained in step g) by adding an aqueous hydroxylated base previously cooled at a temperature lower than 5°C to the cooled chitosan solution until the cooled solution of chitosan exhibits a pH of 6.8-7.2;

i) optionally, increasing the temperature of the neutral cooled solution of chitosan obtained in step h) at a temperature higher than 5°C in order to induce pseudo-thermogelation.

12. (Original) The process according to claim 11, further comprising a step of sterilizing chitosan before the step g) of solubilization.

13. (Currently Amended) The process according to claim 11 ~~or 12~~, wherein in step h), the hydroxylated base is NaOH.

14. (Currently Amended) The process according to ~~anyone of claims 11 to 13~~, further comprising the step of adding an appropriate amount of a diol having a distance of at least 4.7 Å between the hydroxyl groups before, during or after the solubilization step g), or before, during or after the neutralization

step h) to increase the consistency of the hydrogel to the required degree of consistency of the hydrogel.

15. (Original) The process according to claim 14, wherein the diol is 1,3-propanediol.

16. (Currently Amended) The process according to ~~anyone of claims 11 to 15~~, wherein the homogeneously reacetylated chitosan solubilized in step g) is obtained by ~~the process according to claims 7-9~~:

a) filtrating a chitosan having a molecular weight of not smaller than 200 kDa and a deacetylation degree of 80 to 90 % dissolved in an acidic medium to eliminate insoluble particles;

b) precipitating chitosan contained in the filtrated acidic solution obtained in step a) to obtain chitosan free of insoluble particles;

c) preparing a cooled acidic solution of the chitosan free of insoluble particles obtained in step b) at a temperature lower than 5°C to obtain a cooled acidic solution of chitosan free of insoluble particles;

d) preparing a cooled acetic anhydride solution containing a predetermined amount of acetic anhydride in methanol at a temperature lower than 5°C;

e) reacetylating chitosan by adding dropwise, under homogeneous conditions, the cooled acetic anhydride solution of step d) to the cooled solution of chitosan prepared in step c) to provide a crude homogeneously reacetylated chitosan having a deacetylation degree of 30-60 %;

f) treating said crude chitosan obtained in step e) to eliminate salts produced during reacetylation and insoluble particles of chitosan to obtain a homogeneously reacetylated chitosan having a deacetylation degree of 30 - 60 %.

17. (Currently Amended) A phosphate-free transparent pseudo-thermosetting chitosan hydrogel obtained by the process as claimed in ~~anyone~~ of claims 11 to 16.

18. (Currently Amended) A method ~~use of a homogeneously reacetylated chitosan having a deacetylation degree of 30 - 60 % and a molecular weight of not smaller than 200 kD obtained by the process as claimed in claim 7, for the preparation of~~ preparing a phosphate-free, transparent, pseudo-thermosetting chitosan hydrogel comprising using a homogeneously reacetylated chitosan having a deacetylation degree of 30 - 60 % and a molecular weight of not smaller than 200 kD obtained by the process as claimed in claim 7.

19. (Currently Amended) ~~A use of a pseudo-thermosetting neutralized chitosan composition as claimed in claim 1, as a drug delivery system comprising a pseudo-thermosetting neutralized chitosan composition as claimed in claim 1.~~

20. (New) The process according to claim 16, wherein the treating step f) includes the steps of:

f-1) dialyzing chitosan obtained in step e) to eliminate salts produced during reacetylation in order to obtain a homogeneously reacetylated chitosan solution;

f-2) filtrating the chitosan solution obtained in step f-1) to eliminate insoluble particles of chitosan;

f-3) precipitating chitosan contained in the filtrated solution obtained in step f-2) and then drying chitosan to obtain a homogeneously reacetylated chitosan having a deacetylation degree of 30 - 60 %.

21. (New) The process according to claim 20, wherein the precipitating step f-3) includes addition of a mixture of  $\text{NH}_4\text{OH}$ /methanol.

**\*\*\* END CLAIM LISTING \*\*\***



**REMARKS**

The Examiner has imposed a restriction requirement, and requested that Applicants elect one of eight identified groups of claims for prosecution in connection with the present application. The groups of claims are as follows:

- I. Claims 10 and 18, drawn to a homogenously reacylated chitosan.
- II. Claims 1-6 and 19, drawn to a pseudo-thermosetting neutralized chitosan composition.
- III. Claim 17, drawn to a hydrogel.
- IV. Claims 7-9 and 18, drawn to a method of making the invention of Group I.
- V. Claims 16, 18 and 20-21, drawn to a distinct method of making the invention of Group I.
- VI. Claims 11-15 and 19, drawn to a method of making the invention of Group II.
- VII. Claim 18, drawn to a method of using the invention of Group I.
- VIII. Claim 19, drawn to a method of using the invention of Group II.

**APPLICANTS' ELECTION**

Applicants respectfully provisionally elect Group I, Claims 10 and 18, with traverse. Applicants reserve the right to file a divisional application for the non-elected claims during the pendency of this application.

**APPLICANT'S ARGUMENTS**

Applicants respectfully traverse the Restriction Requirement on the grounds that no adequate reasons and/or examples have been provided to support a conclusion of patentable distinctiveness between the identified groups. Restriction is only proper if the claims of the restricted groups are independent or patentably distinct and there would be a serious burden placed on the Examiner of restriction is not required (MPEP § 803). Further, the burden is on the Examiner to provide reasons and/or examples to support any conclusion in regard to patentable distinction (MPEP § 803).

The Examiner asserts that Groups I-VIII do not relate to single general inventive concept under PCT Rule 13.1 and 13.2 because they lack the same corresponding technical feature for the following reasons: "The special technical feature of Group I is a homogenously reacylated chitosan. The special technical feature of instant claim 10 does not present a contribution over the prior art. As disclosed in *Domard et al.* (WO 2002/078760) (...), the technical feature of instant claim 10 is not novel".

Applicants respectfully traverse the Restriction Requirement by contending that *Domard et al.* do not disclose a homogenously reacylated chitosan that meets the limitation of claim 10:

First, *Domard et al.* does not teach a homogenously reacetylated chitosan having a molecular weight of not smaller than 200 kDa and a deacetylation degree of 30-60% (i.e. an acetylation degree of 40-70%) obtained by a process of claim 7.

Further, *Domard et al.* does not teach a process of claim 7 comprising a step (a) of filtrating a chitosan having a molecular weight of not smaller than 200 kDa and a deacetylation degree of 80 to 90% (e.g. an acetylation degree of 10-20%) dissolved in an acidic medium. Nor does *Domard et al.* teach a process of claim 7 further comprising a step (c) of preparing a cooled acidic solution of the chitosan free of insoluble particles obtained in step (b) at a temperature lower than 5°C.

Further, *Domard et al.* does not teach a process of claim 7 comprising a step (d) of preparing a cooled acetic anhydride solution containing a predetermined amount of acetic anhydride in methanol at a temperature lower than 5°C. *Domard et al.* also does not teach a process of claim 7 comprising a step (e) of reacetylating chitosan by adding dropwise under homogenous conditions the cooled anhydride solution of step (d) to the cooled solution of chitosan prepared in step (c) to provide a crude homogeneously reacetylated chitosan having a deacetylation degree of 30-60%.

Finally, *Domard et al.* does not teach that the obtained reacetylated chitosan is homogeneous (homogeneous distribution mode of acetylated and

deacetylated monomers) nor that it is suitable for the preparation of a chitosan neutralized composition, wherein such chitosan preparation would present pseudo-thermosetting properties and would form a transparent hydrogel at a temperature higher than 5°C.

Accordingly, Applicants respectfully submit that the Examiner has not shown that the homogenously reacylated chitosan of claims 1-21 is not a contribution over the prior art.

Applicants also note that claims 1- 21 relate to a single general inventive concept based on a homogenously reacylated chitosan as defined in claim 10 at its intrinsic properties.

For the reasons presented above, Applicants submit that the Examiner has failed to meet the burden necessary in order to sustain the requirement for restriction. Therefore, the Applicants request that the requirement for restriction be withdrawn, and all pending claims including new claims 20 and 21 be rejoined.

**CONCLUSION**

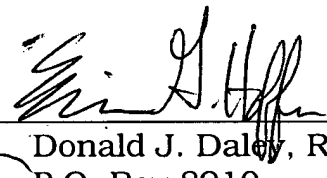
Applicants respectfully request that this application be examined on the merits at the earliest possible time.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Erin G. Hoffman, Reg. No. 57,752, at the telephone number of the undersigned below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2548 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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